REMARKS

Status

Claims 1-66 are pending in this application. Claims 1-6, 11-14, 18, 19, and 21-66 are withdrawn from consideration. Claims 7-10, 15-17, and 20 are currently under examination, with group 311 (SEQ ID NO:471) as the elected species. The Examiner has indicated that the requirement for election of a specific sequence will be rescinded upon allowance of a linking claim (e.g., any of claims 7-10, 15, and 20).

With this reply, Applicants have amended claim 7 to recite SEQ ID NOs: 1-790. Support for this amendment may be found, e.g., in Table 1 (page 6) and at page 12, paragraphs 0029 and 0030. Applicants have also amended claim 20 to independent form. Applicants have replaced the term "tissues" with the term "tissue extracts" in claims 7 and 20 to clarify the antecedent basis.

Information Disclosure Statements

Applicants enclose Form SB/08 and an Information Disclosure Statement under 37 C.F.R. § 1.56 and 1.97(c).

Applicants respectfully note they await confirmation that the Examiner has considered the references listed in the Information Disclosure Statements filed on June 29, 2004, and July 29, 2005 (a courtesy copy of each Form SB/08 is enclosed).

Applicants also note that the Image File Wrapper contains an initialed Form SB/08 from an unrelated application (U.S.S.N. 11/120,435).

Applicants respectfully request that the Examiner provide lists of references submitted by Applicants and considered by the Examiner and remove the unrelated list from the file.

Enablement

The Examiner has rejected claims 7-10, 15-17, and 20 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states that the claims contain subject matter that was not described in the specification in such as way as to enable one skilled in the art to make and/or use the invention.

Without acquiescing to the Examiner's position with respect to enablement of the previously pending claims, Applicants submit that the amended claims are enabled by the specification.

As the Examiner has noted, In re Wands lists eight factors to be considered in determining whether a disclosure satisfies the enablement requirement: (1) the quantity of experimentation required, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5), the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Moreover, "[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. § 2164.04, citing In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants submit that the Examiner's analysis of the Wands factors does not satisfy that burden.

The nature of the invention and the breadth of the claims

The invention is drawn to a method of evaluating the level of neuropathic pain in a mammal by comparing the amount of at least one nucleic acid or protein in a skin

biopsy sample under conditions of neuropathic pain relative to a skin sample under conditions of substantially no neuropathic pain. As noted above, claim 7 states that the nucleic acid or protein comprises a nonredundant subsequence of any one of SEQ ID NOs: 1-790. Claim 20, which is now independent, states that the nucleic acid or protein is muscle-specific.

Applicants respectfully submit that claims do not encompass analysis of "any nucleic acid." Instead, they relate to analysis of nucleic acids and proteins that: (1) comprise a nonredundant subsequence of any one of SEQ ID NOs: 1-790 (claims 7-10 and 15-17); or (2) are muscle-specific (claim 20).

Applicants agree that the claims encompass both increases and decreases in expression of the marker in the neuropathic pain sample relative to the normal sample. However, this "breadth" is entirely consistent with the field in general (expression analysis generally reveals both upregulated and downregulated genes relative to control samples) and, in particular, with Applicants' data. As discussed below, Applicants provide extensive working examples; these examples demonstrate increased expression of some markers and decreased expression of others.

The Examiner's criticism that the claims encompass "any difference in the amount of nucleic acid," "any level of neuropathic pain," and "any mammal" is misplaced. The claims explicitly cover only methods that work, i.e., methods in which the difference detected between the two samples indicates the level of neuropathic pain. "Without undue experimentation or effort or expense the combinations which do not work will be readily discovered and, of course, nobody will use them and the

claims do not cover them." In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976) (emphasis added).

Applicants also note that the Examiner's concerns over the breadth of "any difference" and "any mammal" do not apply to claim 8 (the amount of the nucleic acid differs by at least 2-fold in the two samples), claim 10 (the mammal is a rodent), and 15 (the mammal is a human), respectively.

The amount of guidance presented and the presence or absence of working examples

The specification provides extensive guidance to the skilled artisan, including working examples relevant to the full scope of sequences recited in amended claim 7. Table 2 lists 308 rat nucleic sequences (SEQ ID NOs: 1-308) that Applicants have directly demonstrated to be differentially expressed under conditions of neuropathic pain (relative to a control sample taken under conditions of substantially no neuropathic pain). The remaining SEQ ID NOs recited in amended claim 7 are based on the same data: SEQ ID NOs: 309-470 are rat protein sequences encoded by nucleic acid sequences in SEQ ID NOs: 1-308; SEQ ID NOs: 471-630 and 631-790 are corresponding human nucleic acid and protein sequences. See page 11, paragraph 0026. As shown in Tables 2 through 5, SEQ ID NOs: 1-790 include more than 200 examples of muscle-specific sequences.

The specification also provides extensive and detailed guidance regarding methods for obtaining skin biopsies (page 21, paragraph 0051), animal models of neuropathic pain (page 61, paragraph 57), methods for determining expression levels (pages 21 and 62-64), methods for comparing expression levels and identifying

marker sequences (pages 64-68), and methods for confirming differential expression (pages 68-70).

Quantity of experimentation required

In light of the ample guidance provided in the specification, especially the extensive working examples, the skilled artisan could practice the full scope of the claims with minimal experimentation. Indeed, since Applicants have demonstrated that SEQ ID NOs: 1-308 are surrogate markers of neuropathic pain, the skilled artisan could practice hundreds of embodiments of the claimed methods with no experimentation at all. Hundreds of further embodiments could be practiced after trivially confirming the expectation that the corresponding rat protein sequences, human DNA sequences, and human protein sequences are differentially expressed under conditions of neuropathic pain.

Indeed, practicing the full scope of the claim requires only minimal experimentation: the skilled artisan need only compare SEQ ID NOs: 1-790 to the genome of a mammal of interest to indentify conserved sequences, then perform any of the methods disclosed in the specification and/or known in the art for confirming whether, as expected, the corresponding sequence is differentially expressed under conditions of neuropathic pain.

State of the prior art and relative skill of those in the art

The Examiner has acknowledged that state of the art and the relative skill of those in the art are "high." Office Action of August 15, 2008, at page 6.

Predictability or unpredictability of the art

Applicants respectfully submit that the references cited by the Examiner to support the alleged unpredictability of the art have little or no bearing on the enablement of the claimed methods by the instant specification.

Kroese et al. and Lucentini et al. are wholly irrelevant because both relate to genetic testing. The claimed methods do not involve genetic testing or correlating genetic variants with diseases. Rather, the claims relate to differences in the expression of surrogate markers for neuropathic pain. These references' teachings regarding problems in the art of genetic testing (e.g., the fact that genetic conditions may be caused by more than one gene) simply have no application in expression-based approaches such as those now claimed.

Shalon et al. does relate to expression analysis, but it is not prejudicial to enablement of the claimed methods. The passage cited by the Examiner merely stands for the proposition that expression markers should be identified on the basis of statistically significant differences in expression levels. Shalon states that "standard statistical analyses may be applied to determine when the messenger nucleic acids from a sufficient number of individuals have been evaluated for differences in gene expression." Shalon at page 10, paragraph 0156. As described in Applicants' specification at pages 64-67, Applicants performed "standard statistical analyses" as taught by Shalon. The surrogate markers identified in the instant specification satisfied two separate tests for statistical significance. See page 64 (paragraph 0065) and page 65 (paragraph 0068).

Lovell et al. and Benoliel et al. are also irrelevant. Applicants respectfully submit that the Examiner's characterization of these references as teaching "the unpredictability of determining neuropathic pain within different species of rats" is wholly inaccurate.

Lovell teaches that outbred strain (but not inbred strains) demonstrate significant hyperalgesic responses to peripheral nerve injury. These results do not show "unpredictability of determining neuropathic pain." By all accounts, the inbred strains experienced no neuropathic pain, and the methods employed by Lovell accurately detected no neuropathic pain. The skilled artisan would expect the claimed methods to yield the same accurate determination.

Benoliel states that the "major finding of the present study is that in Lewis but not Sprague-Dawley or Sabra rats a priming trigeminal nerve injury accelerated the development of hindpaw mechanoallodynia and mechanohyperalgesia, following a second sciatic nerve CCI." Pages 208-209, bridge paragraph. Thus, like Lovell, Benoliel simply teaches that some rat strains experienced neuropathy under conditions that caused no neuropathy in other strains. Again, however, there is no teaching of "unpredictability of determining neuropathic pain." Benoliel gives every indication that the methods employed in that study were accurate in detecting neuropathic pain in some rats and no neuropathic pain in others. The Examiner has provided no reason to doubt that the claimed methods would be similarly accurate.

Applicants also note that the Examiner's concern over the alleged unpredictability of practicing the claimed methods in mammals other than rodents and

humans does not apply to claim 10 ("wherein the mammal is a rodent") and claim 15 ("wherein the mammal is a human").

Even if the Examiner had demonstrated that the skilled artisan would not be able to predict which specific sequences will be effective surrogate markers for neuropathic pain in a particular context, such unpredictability would not suffice to prove lack of enablement. Under In re Angstadt, the test for enablement is not whether experimentation would be required for the skilled artisan to make and use the claimed invention, but whether any such experimentation would be undue. 537 F.2d 498 (CCPA 1976). Indeed, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Although the level of predictability in the art to which the invention relates is one of the eight factors in the undue experimentation analysis under In re Wands, the Federal Circuit has explicitly rejected the notion that the skilled artisan must be able to predict with reasonable certainty which experiments will yield the claimed product:

> "If . . . the disclosure must provide 'guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction, whether the claimed product will be obtained, ' as the dissent claims, then all 'experimentation' is 'undue', since the term 'experimentation' implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act." In re Angstadt, 537 F.2d at 503 (emphasis in the original).

In this regard, the instant application compares favorably with the facts of Wands. In that case, the skilled artisan had no basis whatsoever for predicting which

hybridomas would fall within the scope of the claim. Nonetheless, the Federal Circuit found the claims enabled because the specification and the art taught assays though which the claimed hybridomas could be identified without undue experimentation. Here, the skilled artisan starts with the disclosed sequences and need only perform routine experiments to confirm which of these sequences are effective surrogate markers for neuropathic pain in a particular context.

Summary

The Wands factors dramatically support the conclusion that the amended claims are enabled. The breadth of the claims is no more than commensurate with the disclosure; the amended claims recite specific SEQ ID NOs and sequences that are muscle-specific. Applicants' specification provides extensive guidance, including working examples for each of the rat sequences recited in the claim. The recited human sequences are homologous to the rat markers identified in the working examples. Thus, the skilled artisan could practice hundreds of embodiments in rats with no experimentation at all; the efficacy of hundreds of human embodiments could be confirmed with a single array-based experiment on human samples. The Examiner has acknowledged that the state of the art was advanced and that the relative skill of those in the art was high. The references cited by the Examiner to show unpredictability in the art are largely inapposite; moreover, the skilled artisan need not be able to predict which sequences will be effective surrogate markers if they can be identified with merely routine experimentation.

In view of the foregoing, Applicants submit that the Examiner has not met the burden of providing a reasonable basis for questioning the enablement of the claimed

invention. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Novelty

The Examiner has rejected claims 7, 9, 15, and 20 under 35 U.S.C. §102(b) as allegedly anticipated by Terenghi et al. The Examiner states that Terenghi teaches an increase in trkA mRNA expression in skin calf biopsies from diabetic patients relative to normal patients. The Examiner states that trkA is muscle-specific.

The Examiner has also rejected claims 7-9, 15, and 20 under 35 U.S.C. §102(b) as allegedly anticipated by Diemel et al. The Examiner states that Diemel teaches a 4- to 14-fold increase in NGF mRNA expression in skin biopsies from diabetic patients relative to normal patients. The Examiner also states that Diemel teaches that the increase in NGF indicates the level of neuropathic pain.

Without acquiescing to the Examiner's position that the cited references anticipate the previously pending claims, Applicants submit that the amended claims are novel over Terenghi and Diemel.

Claim 7 relates to a method comprising comparing levels of a nucleic acid or protein comprising a nonredundant subsequence of any one of SEQ ID NOs 1-790. Neither trkA nor NGF (the subjects of Terenghi and Diemel, respectively) are among SEQ ID NOs: 1-790. Thus, neither Terenghi nor Diemel teaches every element of claims 7-19, and these claims are novel over these references.

Claim 20 is also novel over Terenghi and Diemel. Claim 20 states that the nucleic acid or protein is muscle-specific. The Examiner has asserted, without explanation, that the mRNAs taught by the references are muscle-specific. Applicants

respectfully disagree. The references clearly teach that trkA and NFG are expressed, inter alia, by neurons. See Terenghi, pages 33-34, bridge paragraph; and Diemel, pages 113-114, bridge paragraph. Thus, neither Terenghi nor Diemel teaches a muscle-specific nucleic acid or protein, and claim 20 is novel over these references.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and timely allowance of the claims. Applicants invite the Examiner to call the undersigned Applicants' representative with any questions or comments.

Please grant any additional extensions of time required to enter this response and charge any additional fees to deposit account 06-0916.

Respectfully submitted,

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Dated: February 15, 2008

By: _____

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